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Long-Term Risk of Autoimmune and Autoinflammatory Connective Tissue Disorders Following COVID-19

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IMPORTANCE Few studies have investigated the association between COVID-19 and autoimmune and autoinflammatory connective tissue disorders; however, research with long-term observation remains insufficient.

OBJECTIVE To investigate the long-term risk of autoimmune and autoinflammatory diseases after COVID-19 over an extended observation period.

DESIGN, SETTING, AND PARTICIPANTS This retrospective nationwide population-based study investigated the Korea Disease Control and Prevention Agency–COVID-19–National Health Insurance Service (K-COV-N) cohort. Individuals with confirmed COVID-19 from October 8, 2020, to December 31, 2022, and controls identified among individuals who participated in the general health examination in 2018 were included in the analysis.

EXPOSURES Confirmed COVID-19.

MAIN OUTCOMES AND MEASURES Incidence and risk of autoimmune and autoinflammatory connective tissue disorders in patients after COVID-19. Various covariates, such as demographic characteristics, general health data, socioeconomic status, and comorbidity profiles, were balanced using inverse probability weighting.

RESULTS A total of 6 912 427 participants (53.6% male; mean [SD] age, 53.39 [20.13] years) consisting of 3 145 388 with COVID-19 and 3 767 039 controls with an observational period of more than 180 days were included. Alopecia areata (adjusted hazard ratio [AHR], 1.11 [95% CI, 1.07-1.15]), alopecia totalis (AHR, 1.24 [95% CI, 1.09-1.42]), vitiligo (AHR, 1.11 [95% CI, 1.04-1.19]), Behçet disease (AHR, 1.45 [95% CI, 1.20-1.74]), Crohn disease (AHR, 1.35 [95% CI, 1.14-1.60]), ulcerative colitis (AHR, 1.15 [95% CI, 1.04-1.28]), rheumatoid arthritis (AHR, 1.09 [95% CI, 1.06-1.12]), systemic lupus erythematosus (AHR, 1.14 [95% CI, 1.01-1.28]), Sjögren syndrome (AHR, 1.13 [95% CI, 1.03-1.25]), ankylosing spondylitis (AHR, 1.11 [95% CI, 1.02-1.20]), and bullous pemphigoid (AHR, 1.62 [95% CI, 1.07-2.45]) were associated with higher risk in the COVID-19 group. Subgroup analyses revealed that demographic factors, including male and female sex, age younger than 40 years, and age 40 years and older, exhibited diverse associations with the risk of autoimmune and autoinflammatory outcomes. In addition, severe COVID-19 infection requiring intensive care unit admission, the Delta period, and not being vaccinated were associated with higher risk.

CONCLUSIONS AND RELEVANCE This retrospective cohort study with an extended follow-up period found associations between COVID-19 and the long-term risk of various autoimmune and autoinflammatory connective tissue disorders. Long-term monitoring and care of patients is crucial after COVID-19, considering demographic factors, disease severity, and vaccination status, to mitigate these risks.

Editorial

Supplemental content

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The COVID-19 pandemic, triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has presented unparalleled challenges to global health, encompassing both immediate and prolonged medical consequences.[1,2] Although the immediate repercussions of COVID-19, including acute respiratory distress syndrome, cardiovascular issues, and acute kidney failure, are well established,[3-5] its extended effects, particularly autoimmune and autoinflammatory diseases, are not fully understood.

COVID-19 is associated with autoimmune diseases, as SARS-CoV-2 potentially interferes with self-tolerance mechanisms in the body and triggers autoimmune responses through cross-reactivity, potentially resulting in the onset of autoimmune diseases.[6] Notably, a variety of autoantibodies, including anti-cyclic citrullinated peptide antibodies linked to psoriasis, inflammatory arthritis, and Graves disease and antinuclear antibodies associated with Guillain-Barré syndrome, have been discovered in individuals who have contracted SARS-CoV-2.[7]

Recent research indicates that COVID-19 could increase the risk of several autoinflammatory connective tissue diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), vasculitis, Crohn disease, and alopecia areata.[8,9] Nevertheless, most of these studies involved a short follow-up period and were inadequate for assessing the development of autoimmune diseases that generally have indolent onset and slow development, thereby underscoring the need for a long-term risk assessment. Therefore, this study investigated the long-term risk of autoimmune and autoinflammatory diseases after COVID-19 using an extended observational period.

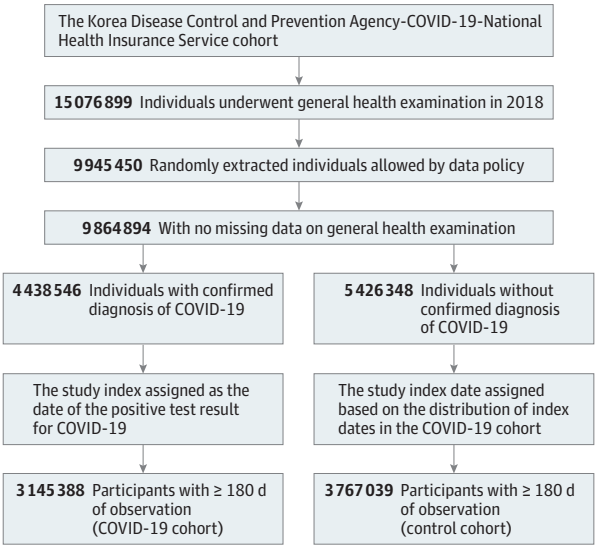
Key Points

Question Is COVID-19 infection associated with an increased long-term risk of autoimmune and autoinflammatory connective tissue disorders?

Findings This cohort study analyzing 6 912 427 participants in South Korea, including 3 145 388 with COVID-19 and 3 767 039 controls observed for more than 180 days, revealed significantly increased risks of various autoimmune and autoinflammatory connective tissue disorders following COVID-19, especially among individuals with severe COVID-19 infection, those infected with the Delta variant, and unvaccinated individuals.

Meaning These findings suggest that long-term monitoring and management of patients is crucial after COVID-19, considering demographic factors, disease severity, and vaccination status, to mitigate these risks.

Figure 1. Study Population Selection


The Korea Disease Control and Prevention Agency-COVID-19-National Health Insurance Service cohort
15 076 899 Individuals underwent general health examination in 2018
9 945 450 Randomly extracted individuals allowed by data policy
9 864 894 With no missing data on general health examination
4 438 546 Individuals with confirmed diagnosis of COVID-19
5 426 348 Individuals without confirmed diagnosis of COVID-19
The study index assigned as the date of the positive test result for COVID-19
The study index date assigned based on the distribution of index dates in the COVID-19 cohort
3 145 388 Participants with ≥ 180 d of observation (COVID-19 cohort)
3 767 039 Participants with ≥ 180 d of observation (control cohort)

Methods

Data Source

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and was approved by the Korean National Bioethics Committee for the use of anonymized data. The National Health Insurance Service (NHIS) of Korea encompasses more than 99% of the Korean population and provides comprehensive patient information, including socioeconomic status, use of health care services, diagnostic records, medical procedures undergone, and prescribed medications.[10] The Korea Disease Control and Prevention Agency COVID-19 registry aggregates detailed information on confirmed COVID-19 cases, including dates of diagnosis, modes of transmission, and COVID-19 vaccination profiles. In South Korea, COVID-19 was confirmed exclusively through polymerase chain reaction (PCR) testing prior to March 2022. However, from March 2022 onwards, physician-confirmed positive results from rapid antigen tests (RATs) were also recognized as confirmed cases. Individuals with positive RAT results or close contact with infected individuals were strongly recommended to visit a health care facility for confirmation. Therefore, the database includes cases with either PCR-positive results or physician-confirmed RAT-positive results. The primary cohort was established by combining the NHIS and the Korea Disease Control and Prevention Agency databases (K-COV-N). The requirement for informed consent was waived by the Korean National Bioethics Committee owing to the use of deidentified data.

Study Population

Individuals who underwent a general health examination in 2018 were initially identified from the K-COV-N cohort, totaling 15 076 899 participants (**Figure 1**). The general health examination conducted by the Korean government is offered every 1 or 2 years to employees, householders, and individuals older than 40 years. This examination includes a variety of health assessments, including blood and urine tests and anthropometric evaluations. It also collects data on individuals' lifestyles and behaviors via structured questionnaires.[11] Due to the data provider's policy regarding data capacity and privacy concerns, a subset of 9 945 450 individuals was randomly extracted for analysis without any selection criteria.

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After removing records with incomplete health-screening data, the final cohort was refined to include 9 864 894 participants. Among 4 438 546 individuals with confirmed COVID-19 from October 8, 2020, to December 31, 2022, a total of 3 145 388 participants with an observational period of longer than 180 days were selected for the COVID-19 cohort. The date of the confirmed positive COVID-19 test result was used as the index date for the COVID-19 cohort. A total of 3 767 039 participants from 5 426 348 individuals without a confirmed diagnosis of COVID-19 were included in the control cohort with an observational period of more than 180 days. To match the observational period between the 2 cohorts, we randomly set the index dates of individuals in the control cohort to reflect the distribution of index dates in the COVID-19 cohort and ensure an equal enrollment ratio on specific dates across both groups.

Outcomes

We assessed the incidence and risk of autoimmune and autoinflammatory diseases in both cohorts. Participants were observed from their respective index dates until the diagnosis of each outcome disease, emigration, death, or the end of the study period (December 31, 2022). Participants with a history of the target outcome before the index date were excluded. Disease occurrence was determined by a minimum of 3 medical visits, either inpatient or outpatient, coded using the corresponding *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*). To confirm the validity of our cohort and analysis, we considered cardiovascular diseases, such as heart failure, which is associated with COVID-19, as positive control outcomes, whereas conditions less likely to be associated with COVID-19, such as epidermal cysts, served as negative controls. *ICD-10* codes for all outcomes are listed in eTable 1 in Supplement 1.

Covariates Control

Demographic, socioeconomic, lifestyle, and comorbidity data were obtained from the NHIS database. We selected covariates based on previous research on the biological plausibility of associations detailed in eMethods in Supplement 1.[8,12-14] The covariates were balanced between the 2 cohorts using inverse probability of treatment weighting (IPTW) and then applied to further adjust the multivariable models.

Statistical Analysis

We used IPTW for the variables indicated in the eMethods in Supplement 1 to mitigate confounding factors between the study groups. Weighting scores were calculated as the probability of inclusion in the COVID-19 cohort divided by 1 minus the probability of inclusion in the COVID-19 cohort, and covariate balance was assessed using the standardized mean differences before and after weighting. Statistical analyses were conducted using multivariable Cox proportional hazards models with adjustments for all predefined covariates used for IPTW, as individuals diagnosed with the target outcome before the index date were excluded from each analysis. Subgroup analyses were conducted based on variables, such as age, sex, COVID-19 severity (requiring intensive care unit [ICU] admission vs not requiring ICU admission), SARS-CoV-2 genotype, and vaccination status. As individual genotypes for SARS-CoV-2 infections were not available in our database, we analyzed the data based on periods dominated by Omicron or Delta variants as surrogates. The Omicron period was defined as starting in January 2022, when the Omicron variant represented 69.3% of cases, with the preceding period dominated by the Delta variant and termed the Delta period.[15] Vaccine types included were viral vector vaccines (ChAdOx1 [Oxford-AstraZeneca] and Ad26.COV2.S [Janssen-Johnson & Johnson]), messenger RNA vaccines (BNT162b2 [Pfizer BioNTech] and mRNA-1273 [Moderna]), and a protein subunit vaccine (NVX-CoV2373 [Novavax]). Individuals were categorized as completely vaccinated if they adhered to the vaccination protocol authorized by the US Food and Drug Administration for a single vaccine type. Those receiving additional doses beyond this protocol were categorized as receiving booster vaccinations. Conversely, those who did not receive any vaccination were designated as individuals with no vaccination, whereas those who did not complete the established vaccination schedule were termed as having incomplete vaccinations. All statistical evaluations were performed using SAS statistical software, version 9.4 (SAS Institute Inc), and R statistical software, version 3.4.1 (R Project for Statistical Computing), with the threshold for significance set at 2-tailed 5%.

Although we used a reliable database to establish the COVID-19 and control cohort as accurately as possible, issues such as diagnostic methods and underreporting may have led to some controls being inappropriately selected. To address this, we conducted sensitivity analyses by setting the observation period to a time when COVID-19 was not present. To ensure that the control group was representative of a group naive to SARS-CoV-2, we performed sensitivity analyses using a prepandemic historical control cohort. In this analysis, the observational period of the control group was shifted back by 3 years from the assigned index date. The COVID-19 cohort was observed until December 31, 2022, and the historical cohort until December 31, 2019.

Results

Study Population

Data of 3 145 388 individuals diagnosed with COVID-19 and 3 767 039 controls were included in the analysis (Figure 1), for a total of 6 912 427 participants (46.4% female and 53.6% male; mean [SD] age, 53.39 [20.13] years). All individuals were observed for a minimum of 180 days. The baseline demographic and general health characteristics of each cohort are summarized in the **Table**, with additional details provided in eTables 2-4 in Supplement 1. The evaluation of covariate balance following IPTW application indicated that the covariates were adequately balanced (eFigure 1 in Supplement 1). The mean (SD) follow-up times for the COVID-19 and control cohorts were 287.6 (47.6) days and 287.7 (47.9) days, respectively.

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Table. Demographic and General Health Characteristics of the Participants Before and After Inverse Probability Treatment Weighting

Characteristics	No. (unweighted %) of patients		SMD	Weighted % of patients		SMD
	COVID-19 cohort (n = 3 145 388)	Control cohort (n = 3 767 039)		COVID-19 cohort (n = 6 930 098)	Control cohort (n = 6 911 596)	
Age, mean (SD), y	50.76 (13.90)	55.40 (14.01)	0.332	53.45 (21.3)	53.34 (19.12)	0.008
Age group, y						
<40	1 534 234 (48.78)	1 252 618 (33.25)	NA	41.06	39.18	NA
40-59	1 277 799 (40.62)	1 877 465 (49.84)	NA	44.16	46.92	NA
>60	333 355 (10.60)	636 956 (16.91)	NA	14.78	13.89	NA
Sex						
Male	1 592 382 (50.63)	2 115 463 (56.16)	0.111	53.58	53.49	0.002
Female	1 553 006 (49.37)	1 651 576 (43.84)		46.42	46.51	
Income level quartile[a]						
Highest	473 776 (15.06)	637 856 (16.93)	0.055	16.71	15.78	0.003
Higher	764 254 (24.30)	935 783 (24.84)		24.27	25.05	
Lower	910 756 (28.96)	1 058 910 (28.11)		27.89	28.80	
Lowest	996 602 (31.68)	1 134 490 (30.12)		31.14	30.37	
Area of residence						
Urban	1 730 055 (55.00)	2 148 850 (57.04)	0.055	56.07	56.05	0.000
Rural	1 415 333 (45.00)	1 618 189 (42.96)		43.93	43.95	
Lifestyle factors						
Current smoker	599 938 (19.07)	724 778 (19.24)	0.004	19.18	19.20	0.001
Alcohol consumption[b]	2 091 249 (66.49)	2 301 280 (61.09)	0.112	63.21	63.34	0.003
No. of health care encounters/y, mean (SD)	14.67 (16.42)	15.24 (17.79)	0.033	15.15 (23.87)	15.19 (26.75)	0.001
Underlying disease						
Hypertension	801 698 (25.49)	1 231 262 (32.69)	0.159	29.77	29.54	0.005
Diabetes	437 132 (13.90)	674 583 (17.91)	0.110	16.36	16.18	0.005
Dyslipidemia	1 196 054 (38.03)	1 650 899 (43.82)	0.118	41.56	41.37	0.004
Atopic dermatitis	31 302 (1.00)	31 304 (0.83)	0.017	0.91	0.91	0.000
Allergic rhinitis	154 477 (4.91)	156 881 (4.16	0.036	4.51	4.52	0.000
Asthma	54 039 (1.72)	67 519 (1.79)	0.006	1.78	1.77	0.000
Hypothyroidism	141 693 (4.50)	158 645 (4.21)	0.014	4.38	4.38	0.000
Hyperthyroidism	49 794 (1.58)	57 714 (1.53)	0.004	1.56	1.56	0.000
Hashimoto thyroiditis	23 904 (0.76)	24 112 (0.64)	0.014	0.70	0.70	0.000
Vitamin D deficiency	136 730 (4.35)	160 589 (4.26)	0.004	4.33	4.33	0.000
Hepatitis B	68 643 (2.18)	83 316 (2.21)	0.002	2.20	2.20	0.000
Hepatitis C	7821 (0.25)	11 740 (0.31)	0.012	0.29	0.29	0.000
HIV infection	161 (0.005)	111 (0.003)	0.001	0	0	0.000

Abbreviations: NA, not applicable; SMD, absolute standardized mean difference.

[a] Divided into quartiles based on health insurance premiums.

[b] Defined as individuals who have consumed alcohol routinely, regardless of the amount or frequency.

Autoimmune and Autoinflammatory Connective Tissue Disorders After COVID-19

The cumulative incidence of autoinflammatory and autoimmune connective tissue disorder outcomes is shown in eFigure 2 in Supplement 1. The incidence and risk of the predefined diseases were assessed during the follow-up period (**Figure 2**). The analysis revealed significantly increased risks associated with COVID-19 for alopecia areata (adjusted hazard ratio [AHR], 1.11 [95% CI, 1.07-1.15]), alopecia totalis (AHR, 1.24 [95% CI, 1.09-1.42]), vitiligo (AHR, 1.11 [95% CI, 1.04-1.19]), Behçet disease (AHR, 1.45 [95% CI, 1.20-1.74]), Crohn disease (AHR, 1.35 [95% CI, 1.14-1.60]), ulcerative colitis (AHR, 1.15 [95% CI, 1.04-1.28]), RA (AHR, 1.09 [95% CI, 1.06-1.12]), SLE (AHR, 1.14 [95% CI, 1.01-1.28]), Sjögren syndrome (AHR, 1.13 [95% CI, 1.03-1.25]), ankylosing spondylitis (AHR, 1.11 [95% CI, 1.02-1.20]), and bullous pemphigoid (AHR, 1.62 [95% CI, 1.07-2.45]).

Age- and Sex-Stratified Analysis

Men diagnosed with COVID-19 exhibited a significantly higher risk of developing alopecia areata (AHR, 1.12 [95% CI, 1.07-1.17]), vitiligo (AHR, 1.24 [95% CI, 1.12-1.37]), Behçet disease (AHR, 1.41 [95% CI, 1.05-1.90]), Crohn disease (AHR, 1.55 [95% CI, 1.25-1.93]), ulcerative colitis (AHR, 1.31 [95% CI, 1.14-1.50]), RA (AHR, 1.11 [95% CI, 1.06-1.16]), SLE (AHR, 1.36 [95% CI, 1.08-1.72]), and ankylosing spondylitis (AHR, 1.14 [95% CI,

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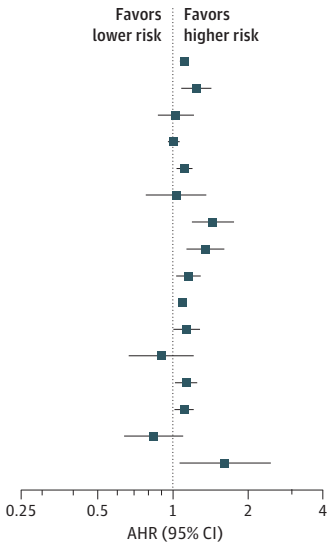
Figure 2. Comparison of Autoimmune and Autoinflammatory Disease Incidence Risks Between the COVID-19 and Control Cohorts

Source	Cohort incidence rate (No. of events/person-years) COVID-19	Control	AHR (95% CI)
Alopecia areata	13.51 (3301/2 442 664)	10.43 (3060/2 933 357)	1.11 (1.07-1.15)
Alopecia totalis	0.92 (228/2 474 400)	0.68 (203/2 965 056)	1.24 (1.09-1.42)
Primary cicatricial alopecia	0.57 (140/2 474 459)	0.53 (158/2 964 924)	1.03 (0.87-1.21)
Psoriasis	5.94 (1456/2 450 391)	6.10 (1791/2 934 069)	1.01 (0.96-1.06)
Vitiligo	3.32 (820/2 468 554)	3.03 (896/2 958 683)	1.11 (1.04-1.19)
Sarcoidosis	0.19 (47/2 475 786)	0.20 (58/2 966 492)	1.03 (0.79-1.35)
Behçet disease	0.52 (128/2 473 479)	0.34 (100/2 964 315)	1.45 (1.20-1.74)
Crohn disease	0.59 (146/2 474 402)	0.42 (126/2 965 272)	1.35 (1.14-1.60)
Ulcerative colitis	1.37 (339/2 470 689)	1.12 (332/2 961 302)	1.15 (1.04-1.28)
Rheumatoid arthritis	19.13 (4599/2 403 967)	18.68 (5378/2 878 387)	1.09 (1.06-1.12)
Systemic lupus erythematosus	1.11 (274/2 472 696)	0.92 (272/2 963 149)	1.14 (1.01-1.28)
Systemic sclerosis	0.16 (39/2 475 847)	0.17 (51/2 966 388)	0.90 (0.67-1.21)
Sjögren syndrome	1.55 (384/2 471 985)	1.45 (429/2 961 440)	1.13 (1.03-1.25)
Ankylosing spondylitis	2.20 (542/2 469 005)	1.99 (590/2 959 193)	1.11 (1.02-1.20)
Dermatopolymyositis	0.19 (47/2 475 844)	0.22 (66/2 966 480)	0.84 (0.64-1.09)
Bullous pemphigoid	0.08 (21/2 476 229)	0.08 (23/2 966 959)	1.62 (1.07-2.45)



Hazard estimates were adjusted for all 27 covariates used in the inverse probability of treatment weighting. AHR indicates adjusted hazard ratio.

1.02-1.28]) than those in the control group (**Figure 3** and eFigures 3-6 in Supplement 1). Women exhibited an increased risk of alopecia areata (AHR, 1.09 [95% CI, 1.03-1.15]), alopecia totalis (AHR, 1.32 [95% CI, 1.07-1.64]), Behçet disease (AHR, 1.47 [95% CI, 1.16-1.87]), RA (AHR, 1.07 [95% CI, 1.04-1.11]), and bullous pemphigoid (AHR, 2.11 [95% CI, 1.20-3.68]). In the age stratification, individuals younger than 40 years exhibited higher risks of alopecia areata (AHR, 1.20 [95% CI, 1.12-1.28], primary cicatricial alopecia (AHR, 1.54 [95% CI, 1.03-2.30]), Behçet disease (AHR, 1.66 [95% CI, 1.05-2.63]), and ulcerative colitis (AHR, 1.35 [95% CI, 1.09-1.69]), whereas those 40 years or older were more likely to develop alopecia areata (AHR, 106 [95% CI, 1.02-1.11]), alopecia totalis (AHR, 1.28 [95% CI, 1.10-1.48]), vitiligo (AHR, 1.10 [95% CI, 1.02-1.18]), Behçet disease (AHR, 1.40 [95% CI, 1.14-1.72]), Crohn disease (AHR, 1.44 [95% CI, 1.19-1.76]), RA (AHR, 1.10 [95% CI, 1.07-1.13]), SLE (AHR, 1.25 [95% CI, 1.09-1.42]), Sjögren syndrome (AHR, 1.15 [95% CI, 1.04-1.27]), ankylosing spondylitis (AHR, 1.12 [95% CI, 1.02-1.23]), and bullous pemphigoid (AHR, 1.63 [95% CI, 1.07-2.46]).

Severity of COVID-19 and Vaccination Status

Among individuals with severe COVID-19 requiring ICU admission, the risk of autoimmune diseases, including alopecia areata (AHR, 1.21 [95% CI, 1.03-1.43]), psoriasis (AHR, 1.33 [95% CI, 1.11-1.60]), sarcoidosis (AHR 4.12 [95% CI, 2.28-7.43]), Behçet disease (AHR, 2.59 [95% CI, 1.53-4.38]), Crohn disease (AHR, 1.84 [95% CI, 1.03-3.29]), ulcerative colitis (AHR, 2.43 [95% CI, 1.74-3.41]), RA (AHR, 1.27 [95% CI, 1.15-1.41]), SLE (AHR, 2.22 [95% CI, 1.55-3.16]), Sjögren syndrome (AHR, 2.85 [95% CI, 2.22-3.66]), ankylosing spondylitis (AHR, 1.42 [95% CI, 1.06-1.92]), and bullous pemphigoid (AHR, 6.82 [95% CI, 3.59-12.93]), was significantly higher than that in the control group (**Figure 4** and eFigures 7-10 in Supplement 1). This pattern was also observed in the general ward and outpatient group, although the effect size tended to be lower. In the stratified analysis by COVID-19 period, the risks of alopecia areata (AHR, 1.37 [95% CI, 1.22-1.53]), alopecia totalis (AHR, 2.51 [95% CI, 1.75-3.59]), psoriasis (AHR, 1.50 [95% CI, 1.29-1.74]), Behçet disease (AHR, 1.90 [95% CI, 1.14-3.17]), Crohn disease (AHR, 1.94 [95% CI, 1.18-3.21]), ulcerative colitis (AHR, 2.47 [95% CI, 1.88-3.23]), RA (AHR, 1.43 [95% CI, 1.31-1.56]), SLE (AHR, 2.50 [95% CI, 1.87-3.33]), Sjögren syndrome (AHR, 2.12 [95% CI, 1.64-2.75]), and ankylosing spondylitis (AHR, 1.34 [95% CI, 1.03-1.73]) were significantly higher in the Delta-dominant period. Although a similar pattern was observed during the Omicron-dominant period, the extent of the risk was generally lower (Figure 4). In the stratification by vaccination status, individuals who were not vaccinated exhibited a higher risk of developing various autoimmune diseases, including alopecia areata, alopecia totalis, psoriasis, Behçet disease, Crohn disease, ulcerative colitis, RA, SLE, Sjögren syndrome, and ankylosing spondylitis, whereas vaccinated individuals exhibited comparable or lower effect sizes for most outcomes (eFigures 11-15 in Supplement 1).

Validation With Control Outcomes

To ensure the robustness of our findings, we examined the risks associated with both positive and negative control outcomes in relation to COVID-19 (eFigure 16 in Supplement 1). For the positive control outcomes, the risk of heart failure (AHR, 1.12 [95% CI, 1.09-1.15]) was significantly higher in the COVID-19 cohort than in the control cohort. Furthermore, consistent with previously reported studies, the risk of heart failure was significantly higher in those with ICU admission (AHR, 3.00 [95% CI, 2.83-3.18]) and during the Delta-dominant period (AHR, 1.87 [95% CI, 1.74-2.01]) compared with those receiving general ward or outpatient care and those in the Omicron period.[16,17] On the other hand, the risk of negative control outcomes, such as epidermal cysts, did not show a significant increase in the COVID-19 cohort compared with the control cohort (AHR, 0.99

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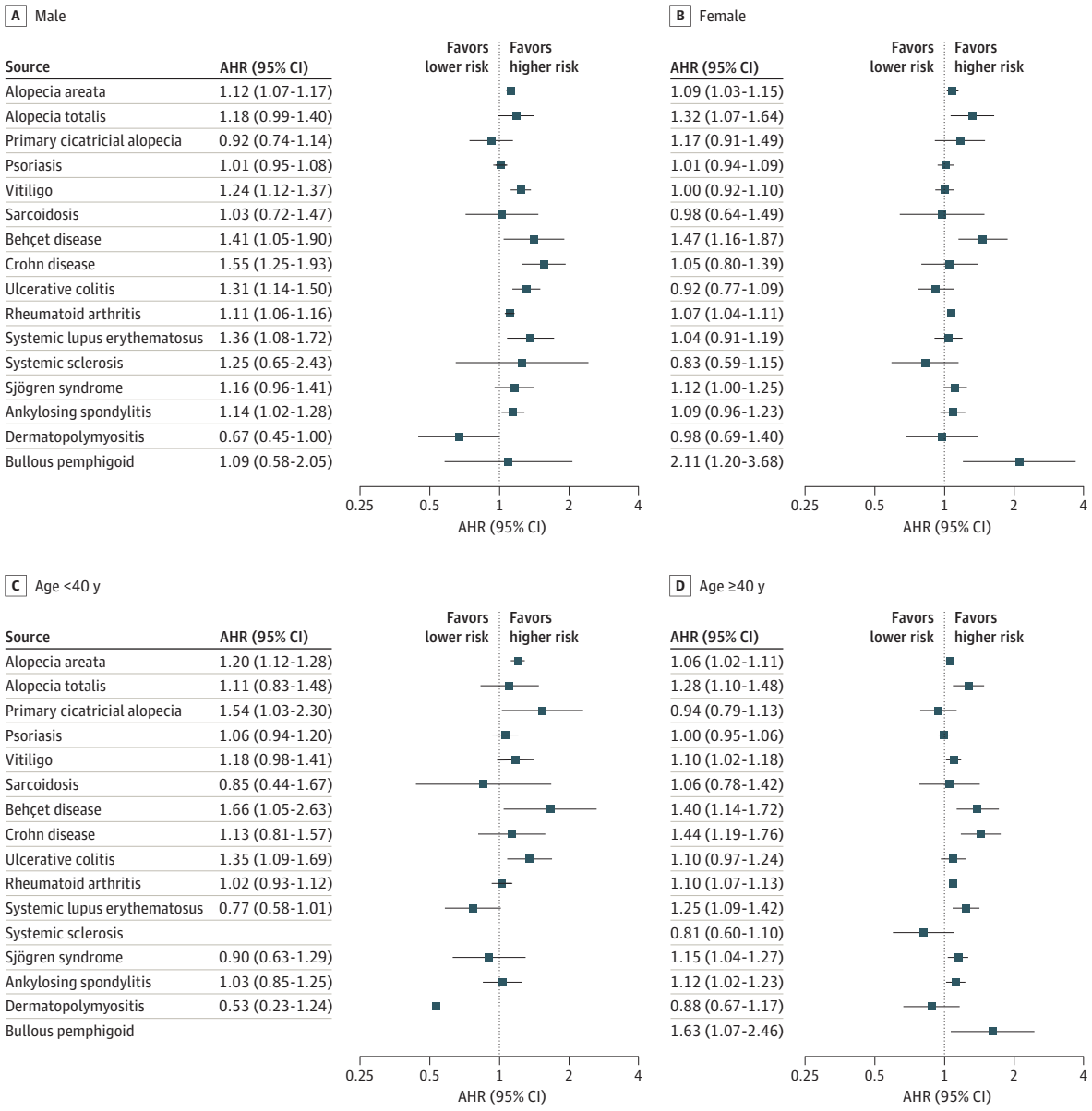
Figure 3. Autoimmune and Autoinflammatory Disease Risk by Age and Sex in the COVID-19 and Control Cohorts



Hazard estimates were adjusted for all 27 covariates used in the inverse probability of treatment weighting. AHR indicates adjusted hazard ratio.

[95% CI, 0.96-1.01]), except during the Delta-dominant period (AHR, 1.10 [95% CI, 1.02-1.20]).

Sensitivity Analyses

In the sensitivity analyses with the historical control cohort, patients with COVID-19 demonstrated a higher risk of developing alopecia areata, alopecia totalis, vitiligo, SLE, ankylosing spondylitis, and bullous pemphigoid compared with the historical control group (eFigure 17 in Supplement 1). Overall, there was a similar increased risk of various autoimmune diseases, consistent with findings in the contemporary control group, despite variations in statistical significance and effect size for specific diseases.

Discussion

This cohort study with an extended follow-up period revealed an increased long-term risk of autoimmune and autoinflammatory connective tissue disorders, including alopecia areata, alopecia totalis, vitiligo, Behçet disease, Crohn disease, ulcerative colitis, RA, SLE, Sjögren syndrome, ankylosing spondylitis, and bullous pemphigoid after COVID-19. Subgroup analyses showed that demographic factors exhibited diverse effects on the risk of autoimmune and autoinflammatory outcomes. In addition, severe COVID-19, the Delta genotype, and no-vaccination status were associated with a higher risk.

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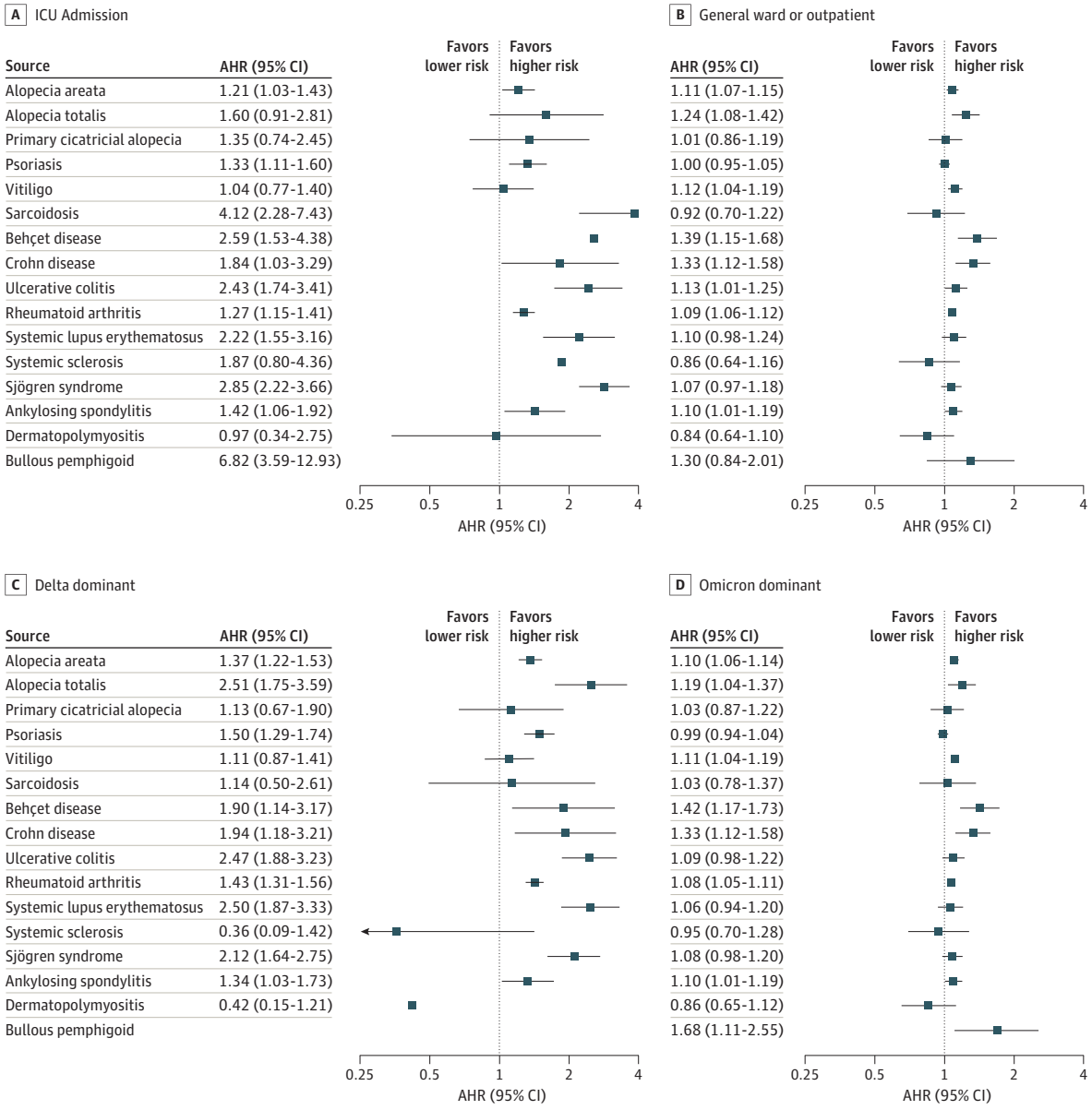
Figure 4. Autoimmune and Autoinflammatory Disease Risk in the COVID-19 Cohort by COVID-19 Severity and Period



Hazard estimates were adjusted for all 27 covariates used in the inverse probability of treatment weighting. The absence of the adjusted hazard ratio (AHR) and 95% CIs for bullous pemphigoid in panel C is not due to missing data but is a result of low sample size and insufficient events in this subgroup. ICU indicates intensive care unit.

A previous study from our group,[8] involving 354 527 individuals with COVID-19, suggested an increased risk of autoimmune disorders, such as alopecia areata, alopecia totalis, antineutrophil cytoplasmic antibody-associated vasculitis, Crohn disease, and sarcoidosis. However, the follow-up period (120 days) was relatively short, thereby limiting the assessment of slow-onset autoimmune diseases. Therefore, the present study included extended follow-up periods, ensuring a minimum of 180 days of follow-up for all participants, with a mean duration of 287 days. Compared with previous studies,[8,9] our research identified additional associations with various diseases, including SLE, vitiligo, Behçet disease, RA, Sjögren syndrome, ankylosing spondylitis, and bullous pemphigoid.

Notably, COVID-19 severity was associated with a high risk of autoimmune diseases. COVID-19 has been associated with significantly elevated levels of proinflammatory cytokines and chemokines.[18] Moreover, levels of certain cytokines, including interleukin (IL) 1, IL-6, IL-10, and IL-18, have been associated with disease severity.[19-21] Therefore, the cytokine storm and immune dysregulation following COVID-19 infection may play a role in the pathogenesis of autoimmune diseases.

Consistent with previous studies,[22,23] our study found a lower risk of autoimmune diseases during the Omicron pe-

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riod than during the Delta period. Notably, lower pathogenicity of Omicron variants than the Delta variants has been found in both clinical and animal studies,[24-26] which supports our findings. Compared with vaccinated individuals, the unvaccinated group demonstrated a higher risk of autoimmune and autoinflammatory diseases. This aligns with a recent study[27] that exclusively analyzed unvaccinated individuals and suggested an increased risk of various autoimmune diseases. These findings may provide evidence to support the hypothesis that COVID-19 vaccines can help prevent autoimmune diseases.[9]

Consistent results across studies support the hypothesis that COVID-19 triggers autoimmune processes through mechanisms such as molecular mimicry, cross-reactive antibodies, and increased autoantibodies.[6,28-31] Additionally, the presence of angiotensin-converting enzyme 2 receptors, immune cell activation, and tissue damage may contribute to autoimmune disease development after COVID-19.[32-35] This suggests that SARS-CoV-2 might operate via various mechanisms. However, further research is warranted to elucidate specific pathways.

Several studies[36-40] have highlighted the impact of COVID-19 on rheumatic diseases, revealing that the virus induces an imbalance in cytokines and chemokines similar to those observed in SLE and RA.[41] Additionally, transcriptomic analysis has revealed potential biomarkers linking Behçet disease to COVID-19, suggesting a close association between viral infections and autoimmune responses.[42] Studies suggest that SARS-CoV-2 may trigger gland inflammation, leading to Sjögren syndrome–specific autoantibodies and cause conditions like interstitial pneumonia and myocarditis, similar to those seen in lupus and Sjögren syndrome.[43,44]

Meanwhile, other research points to the development of dermatological autoimmune conditions following COVID-19. Notably, vitiligo after COVID-19 infection has also been reported.[45,46] Vitiligo, often associated with genetic predispositions and infections like cytomegalovirus, Epstein Barr virus, and HIV, is triggered by oxidative stress and immune dysregulation.[47,48] Dysregulation of $CD8^+$ lymphocytes, oxidative stress, and temporary immunosuppression by SARS-CoV-2 constitute another potential link between vitiligo and COVID-19.[46,49] Similarly, cases of bullous pemphigoid following COVID-19 have demonstrated virus-induced activation of IL-17, leading to the disruption of hemidesmosomes and severe skin manifestations.[50-52] These findings underscore the complex interactions between COVID-19 and autoimmune conditions, necessitating further research to fully understand postinfection complications.

Strengths and Limitations

Our study has several strengths. First, the follow-up period of 287 days on average was considerably longer than that of previous studies, ensuring adequate time to observe the progression and outcomes of autoimmune diseases. Second, we used comprehensive national data encompassing the medical records of approximately 7 million individuals, along with detailed information on COVID-19 infections and vaccination histories. Third, we conducted analyses addressing diverse covariates, such as demographic, anthropometric, and lifestyle factors, complemented by both positive and negative controls. Fourth, stratified analyses based on parameters, including age, sex, severity, genotype, and vaccination status, not only reaffirmed the associations we identified but also helped identify vulnerable subgroups.

Nevertheless, this study also has limitations. First, our study population consisted of a single ethnicity, which may have limited the generalizability of our findings. In addition, our dataset did not include comprehensive details on individual aspects such as genetic predisposition. Second, correction for potential confounders was constrained by the variables available in the dataset. Third, despite analyzing a nationwide database that reliably included patients diagnosed through PCR or RAT with physician confirmation, a residual selection bias remains for individuals who were never tested or did not report to a health care clinician, potentially leading to overestimation or underestimation of the findings. For example, patients with unreported or asymptomatic COVID-19 in the control group could reduce the contrast between the COVID-19 and control groups, thereby diminishing the effect size. Conversely, if patients with mild or asymptomatic COVID-19 were missing from the COVID-19 group, the inclusion of relatively severe cases could have resulted in an overestimation of the risk of outcome diseases. However, we sought to ensure the accuracy and robustness of our findings through validation of the historical control and control outcomes. Finally, the relatively low incidence rates of certain diseases necessitate cautious interpretation of statistical significance. Although an increased risk was clearly observed for certain diseases in severe cases of COVID-19, the overall results showed that the risk for many conditions was not considerably high. Given the low incidence rates, the clinical significance of these findings may be limited. However, since this increasing pattern was consistently observed across various conditions even in mild cases of COVID-19, further research is needed to determine whether SARS-CoV-2 infection contributes to a long-term increase in autoimmunity traits.

Conclusions

This cohort study comprehensively examined the long-term risks of autoimmune and autoinflammatory connective tissue disorders in patients with COVID-19, underscoring the potential sequelae following COVID-19 and the need for continued vigilance and research on the autoimmune consequences of COVID-19. Understanding the specific vulnerabilities and disease patterns among different subgroups is crucial for mitigating the long-term impact of the pandemic on global health.

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